# Exhibit 7

| **Establishment Inspection Report** | FEI: | **3003999190** |
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| Zhejiang Huahai Pharmaceutical | EI Start: | 06/24/2019 |
| Linhai, Zhejiang, 317024, China | EI End: | 06/28/2019 |

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## SUMMARY

This report details a pre-announced, Pre-Approval Inspection (PAI) of Zhejiang Huahai Pharmaceutical, an Active Pharmaceutical Ingredient (API) and Drug Product (DP) manufacturer. This inspection was performed under eNSpect OP ID 118918, Trip 2019-378S, per request by CDER's Office of Process and Facilities (OPF) and OIP China's FY19 Drug Workplan. I conducted the inspection per CPGM 7346.832, "Pre-Approval Inspections" and used ICH Q7 as reference material. Coverage during the inspection include the three PAI objectives: 1) Readiness for Manufacturing, 2) Conformance to the Application, and 3) Data Integrity Audit. Profile Class Code coverage included initial coverage for SVS – Sterile-Filled Small Volume Parenteral Drugs and LMS – Laboratory, Microbiological-Sterility Testing. The following historic profile class codes were not updated as part of this inspection as they were covered and updated during the previous FDA inspection performed 05/20-31/2019, including: CHG – Capsules, Prompt Release; CSN – Non-Sterile API By Chemical Synthesis; CTR – Capsules, Modified Release; TCM – Tablets, Prompt Release; TTR – Tablets, Extended Release; TCT – Tablets, Delayed Release; LCP –



 

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At the close of the inspection on 06/28/2019, a five (5) item FDA 483, Inspectional Observation (**Attachment 1**), was issued to Mr. Baohua Chen, President, and most responsible person at the firm. In addition to the five (5) observations cited on the FDA 483, I also verbally communicated three (3) discussion items with the firm during the inspection and again at the close-out meeting. Management acknowledged the FDA 483 observations and promised to implement corrections. I provided the firm with a handout, in English and translated in Chinese, which provided instructions for electronically submitting the FDA 483 response (**Attachment 2**).

Since 2017, this facility has been involved in three product recalls. These product recalls were filed by Prinston Pharmaceutical, Cranbury NJ, the applicant holder, for which this firm acts as a Contract Manufacturing Organization (CMO) for the products which are the subject of the recall. Product recalls include:

1. Valsartan Tablets, one lot recalled; still on-going
2. Valsartan Tablets and Valsartan and HCTZ Tablets; all lots within expiry recalled; still on-going
3. Irbesartan Tablets and Irbesartan and HCTZ Tablets; eight lots recalled; still on-going

No refusals were encountered and no samples were collected.

Firm's FDA registration is current and effective until 12/31/2019. A review of the firm's registration identified the following business operations were listed: API MANUFACTURE and MANUFACTURE.

**ADMINISTRATIVE DATA**

| | |
|---|---|
| Inspected firm: | Zhejiang Huahai Pharmaceutical |
| Location: | Xunqiao<br>Linhai, Zhejiang, 317024, China |
| Phone: | +86-576-85016003 |
| FAX: | +86-576-85016013 |
| Mailing address: | Xunqiao<br>Linhai, Zhejiang 317024, China |
| Dates of inspection: | 06/24/2019 – 06/28/2019 |
| Days in the facility: | 5 |
| Participants: | **Jonathan W Chapman, Investigator** |

On 06/24/2019, I, investigator Jonathan W. Chapman, displayed my credentials to Baohua Chen, President, who was identified to be the most responsible person at the firm. I also displayed my credentials to the other individuals present at the opening meeting. **Exhibit 1** contains a list of Zhejiang Huahai Pharmaceutical personnel present at the opening meeting. Business cards were exchanged and I explained the purpose of the inspection was to conduct a PAI inspection focused on the activities they perform in support of DMF 029741 Rocuronium Bromide (Drug Substance) and ANDA (b) (4) Rocuronium Bromide Injection (Drug Product).

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On 06/24/2019, a close-out meeting was held with the firm. At the close-out meeting, the firm was represented by Baohua Chen, President, and most responsible person. **Exhibit 2** contains a list of all Zhejiang Huahai Pharmaceutical employees who attended the close-out meeting. A five (5) item FDA 483, Inspectional Observations (**Attachment 1**), was issued to Mr. Chen, President. In addition to the observations listed on the FDA 483, I also verbally communicated three (3) discussion items with the firm's management during the close-out.

No in-plant inspectors or other government agencies were present during this inspection. Dr. Xiaodi Guo, Chief Scientific Officer/EVP for Prinston Pharmaceutical, the applicant holder and U.S. Agent, was present during the inspection.

Please note: interpretation was provided by Mr. Wayne Cheng, Senior Manager, QA throughout the inspection (i.e., 06/24-28/2019). Unless otherwise specified, when I refer to myself speaking with an employee it is through Mr. Cheng.

In addition, for clarity and to ensure consistency in reporting, Zhejiang Huahai Pharmaceutical Co., Ltd, located in Linhai, Zhejiang 317024, China, may be referred to in this report as "the firm", "Huahai", "Huahai Pharmaceutical", "Huahai Xunqiao" "Xunqiao Site", "Xunqiao" and/or "ZHP".

Post inspectional correspondence should be addressed to:

Zhejiang Huahai Pharmaceutical Co., Ltd.
Attention: Mr. Jun Du, Executive Vice President
Xunqiao
Linhai, Zhejiang, 317024, China
Tel: +86-576-85016003
Mobile: +86-13805720633
Email: dujun@huahaipharm.com

**HISTORY**

Refer to **Exhibit 3**, the firm's corporate presentation for an overview of the company and its history.

Zhejiang Huahai Pharmaceutical Co., Ltd is a pharmaceutical company engaged in the development, manufacture, and marketing of APIs and finished dosage formulations for global supply. The firm was established in China in 1989 and is a vertically integrated pharmaceutical company. The firm has three manufacturing sites in China: Xunqiao Site (FEI: 3003999190) which manufactures API intermediates, APIs, and DPs; Chuannan site (FEI: 3003885745) which manufactures APIs and key intermediates; and Huanan Site (No FEI) which manufactures starting materials and intermediates (**Exhibit 3, Page 5**). The Xunqiao Site, which was the focus of this inspection, also acts as the company's corporate headquarters. According to the firm, in 2007, the Xunqiao site became the first finished dosage formulation (FDF) manufacture in China to be approved by the U.S. FDA and in 2009 became the first Chinese company to market a FDF in the U.S. The Xunqiao site's operations are divide into two groups: FDF and API. Refer to **Exhibit 3, Page 9**. for the firm's corporate structure. Refer to **Exhibit 3, Page 14**, for the organizational chart of the Xunqiao FDF Site. Refer to

## INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Refer to **Exhibit 3, Page 14**, for the organizational chart of the Xunqiao FDF Site. Refer to **Exhibit 3, Page 23**, for the organizational chart of the Xunqiao API Site. Refer to **Exhibit 3, Page 30**, for the organizational chart of the Xunqiao Quality Unit.

- **Dr. Baohua Chen, President/Chairman:** was the most responsible person at the firm and was present during the opening meeting of the inspection on 06/24/2019 and close-out meeting on 06/28/2019. Dr. Chen started working for the firm in December 1988 and has been in his current role as President/Chairman since April 2007. His main responsibilities and duties include create the company's development strategy and to implement resolutions of the board of directors. He has the ultimate authority at the firm and takes full responsibility for the company's operations. Dr. Chen, was present during the close-out meeting on 06/28/2019 and the FDA 483 (**Attachment 1**) was issued to him.
- **Mr. Jun Du, Executive Vice President**: Mr. Du reports directly to Mr. Chen and in the absence of Mr. Chen, he is the most responsible person at the facility and assumes all responsibility. His main responsibilities and duties are to ensure the completion of the company's annual performance targets. Mr. Du has worked for Huahai since January 2000 and has been in his current position since April 2013. Mr. Du was present every day of the inspection.
- **Ms. Faye Shang, Vice President of Quality & Qualified Person**: Ms. Shang reports to Dr. Chen. She has worked for Huahai since January 2019 and has been in her current position since April 2019. Ms. Shang is fully responsible for the quality management operations of Huahai. She was present every day of the inspection.

Refer to **Exhibit 10** for additional information such as name, title, and major responsibilities of Xunqiao Site's Senior Management which I interacted with during this inspection.

Refer to **Exhibit 11** for a list of employees I interacted with on a limited basis (e.g., interviewed) throughout the inspection.

The firm identified their U.S. Agent for this PAI product to be:

Prinston Pharmaceutical
Attention: Dr. Xiaodi Guo
2002 Eastpark Blvd
Cranbury, NJ 08512
Tel: +1-609-655-1688
Fax: +1-609-655-1658
Email: xiaodi.guo@prinstonpharm.com

## FIRM'S TRAINING PROGRAM

The firm has a training program with established written procedure and requirements. Procedure SMP-006.04, entitled Corporate Training System, was reviewed during the previous FDA inspection on 05/20-31/2019. Due to time constants, I did not perform an assessment of employee training

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**RECALL PROCEDURES**

The firm has written procedures for performing product recalls. SMP-013.10, entitled Product Recall Management System, Effective Date 2019/5/15. Since January 2018, the firm has been involved in two separate product recalls which involve four drug products, including:

- All lots of Valsartan Tablets and Valsartan/HCTZ Tablets within expiration are currently being recalled
- Eight batches of Irbesartan Tablets (one batch) and Irbesartan/HCTZ Tablets (seven batches) are currently being recalled

For both product recalls, the Xunqiao Site was the CMO of the finished drug product and Prinston Pharmaceutical was the ANDA owner. Per the quality agreement between the two companies, Prinston is responsible for managing the recall and notifying the appropriate authorities. Both recalls were associated with nitrosamine impurities which were detected in Valsartan API and Irbesartan API batches manufactured at Huahai's Chuannan Site.

**OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE**

At the close of the inspection on 06/28/2019, a five (5) item FDA 483, Inspectional observation (**Attachment 1**) was issued to Mr. Baohua Che, President, and most responsible person at the firm. Since most the firm's employees do not speak English, the firm opted to have Mr. Wayne Cheng read the FDA 483 to the Huahai employees present so he could translate. I informed the firm's management present that they could respond in writing to the observations within 15 business days and provided a handout (**Attachment 2**), both in English and translated in Chinese, with detailed instructions on the process for electronically submitting a FDA 483 response. I clarified any questions the firm had regarding the response process and/or FDA 483 observations. Mr. Du and the firm's management acknowledged the observations and stated they intend to submit a written response within 15 business days describing their corrective actions to the cited observations.

**Observations listed on form FDA 483**

**OBSERVATION 1**

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, Deviation Investigations RDF-17038 and RDF-18010 were initiated to investigate white particulates observed during the manufacturing of Rocuronium Bromide Injection, Batches 130217001 and 130217002, respectively. The investigations concluded the probable root cause and likely source of the white particulates were caused by inadequate cleaning of the CIP Skid tanks and pipes (i.e., RDF-17038) and 20mL rotary pump valve (i.e., RDF-18010). However, the investigations into the root cause of the white particulates were incomplete in that they failed to evaluate the identity of the white particulates as part of the investigation into the potential source(s) of their origin.

Reference 21 CFR 211.192

In addition, I asked when unknow peaks are required to be evaluated and was told any peak ≥2% should be evaluated. I asked the firm to reprocess the chromatograms for Lot 1302A18001 (**Exhibit 39**) and Lot 1302A18002 (**Exhibit 40**) without the integration inhibited from 0.00 minutes to 4.00 minutes. Both chromatograms contained a peak within the previously inhibited area that was ≥2%. These peaks were not observed in the typical chromatogram included in the test procedure. The firm noted these were known peak and that is why no further evaluation was performed. A review of the data integrity check record completed for this injection sequence (**Exhibit 41**) noted it fell silent discussing the rationale for the integration parameters selected. It also made no mention that the inhibited peaks observed to be greater than 2% were in fact confirmed to be known peaks. I reiterated my concerns regarding the adequacy of test procedure M-F62601.01, as this procedure did not contain typical chromatograms (e.g., sample solution) for analyst to reference.

**Discussion with Management:**
Mr. Du and the firm's management acknowledged the observation and noted Zhejiang Huahai planned to correct the issues and respond in writing within 15 business days.

## REFUSALS

I did not encounter any refusals during this inspection.

## GENERAL DISCUSSION WITH MANAGEMENT

At the conclusion of the inspection on 06/28/2019, a close-out meeting was held with the firm's management. Exhibit 2 contains a complete list of all Zhejiang Huahai Pharmaceutical employees who attended the close-out meeting. In addition to the five (5) item FDA 483, Inspection Observation, issued to Baohua Chen, President, during the close-out meeting, three (3) discussion items were verbally communicated with Mr. Chen and Huahai Xunqiao's management present.

The discussion items verbally communicated with the firm included:

- **Discussion Item 1: Assessment of Analytical Method for Rocuronium Bromide Injection, Related Substance Testing is Pending:** While performing a data integrity review of related substance stability data for Rocuronium Bromide API, I observed the presence of an unknown peak eluting near the API peak. After some discussion with the firm regarding this peak, the firm provided a report (**Exhibit 49**), entitled Application of Two-dimensional Liquid Chromatography – Tandem Mass Spectrometry in the Identification of RRT 1.09 Impurity in Rocuronium Bromide. The firm noted they recently performed this study to identified the unknown impurity in response to an FDA deficiency letter requesting them to identify the unknown impurity eluting at RT 9.183 min due to its content being greater than 0.05%. The study identified the impurity, referred to as RRT 1.09, as des-morpholine rocuronium. The firm stated they plan to update their specifications to monitor the impurity as a specified, identified impurity with a specification of NMT 0.1%. I expressed concern regarding the suitability of their current related substance test method as the peak resolution

43. **Exhibit 43**: Copy of manufacturing process flow chart for production of Rocuronium Bromide Injection in Workshop VI, 1 page
44. **Exhibit 44**: Copy of media fill batches executed in Workshop VI, 1 page
45. **Exhibit 45**: Copy of Stability Study Protocol for Rocuronium Bromide Injection, Protocol Number Q-04-17-P044, 36 pages
46. **Exhibit 46**: Copy of Stability Study Report for Rocuronium Bromide Drug Substance, ARSP-17-017, dated 2017.06.20, 34 pages
47. **Exhibit 47**: Copy of a list of major equipment in Workshop VI used in the production of Rocuronium Bromide Injection, 1 page
48. **Exhibit 48**: Copy of document, entitled Explanation of improvement of data backup on PMS online particle monitoring system and online pressure control system, 4 pages
49. **Exhibit 49**: Copy of report entitled Application of Two-dimensional Liquid Chromatography – Tandem Mass Spectrometry in the Identification of RRT 1.09 Impurity in Rocuronium Bromide, dated June 24, 2019, 13 pages
50. **Exhibit 50**: Screenshots of chromatograms for 18 month, related substance stability testing for Rocuronium Bromide API, Lots 5276-17-001, 5276-17-002, and 5276-17-003, 4 pages

**ATTACHMENTS**

1. **Attachment 1:** FDA Form 483, Inspectional Observations, issued to Mr. Baohua Chen President of Zhejiang Huahai Pharmaceutical Co., Ltd, Linhai, Zhejiang, 317024, China, Date Issued 06/28/2019, 4 pages
2. **Attachment 2**: Office of Pharmaceutical Quality Operations, "Electronic Submission of FDA-483 Response" handout, both in English and Chinese translations, 3 pages
3. **Attachment 3**: Initial Field Recommendation, 2 pages
4. **Attachment 4**: Copy of a portion of Zhejiang Huahai Pharmaceutical, DMF 029741, Module 3.2.S.2.2, Description of Manufacturing Process and Process Controls, 16 pages

Jonathan W. Chapman -S

Digitally signed by Jonathan W. Chapman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001174613, cn=Jonathan W. Chapman -S
Date: 2019.07.22 15:41:18 +08'00'

Jonathan W. Chapman, Investigator